Oral contraceptive use and glucose metabolism in a national sample of women in the United States

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OBJECTIVE: This study was undertaken to determine whether users of oral contraceptives in a nationally representative population of US women had elevated levels of measures of glucose metabolism.

STUDY DESIGN: Cross-sectional data from the Third National Health and Nutrition Examination Survey (1988-1994) included hemoglobin A_{1c} levels and fasting glucose, insulin, and C-peptide levels. Means were compared among those who had never used oral contraceptives, current users of oral contraceptives, and former users of oral contraceptives, with and without adjustment for potential confounders.

RESULTS: The vast majority of current users of oral contraceptives were using low-dose estrogen formulations. The two most common preparations were a triphasic formulation containing 0.035 mg ethinyl estradiol and 0.5, 0.75, and 1 mg norethindrone (23.9%) and a monophasic formulation containing 0.035 ethinyl estradiol and 1 mg norethindrone (20.7%). Current users of oral contraceptives did not have elevated values for any of the four measures of glucose metabolism. Hemoglobin A_{1c} level and fasting glucose, insulin, and C-peptide levels were not related to duration of current use, age at which use began, or major formulation type. Among women who were former users of oral contraceptives there was no evidence of higher values among those who had recently ceased use.

CONCLUSION: Oral contraceptive formulations currently available in the United States are not associated with an adverse glucose metabolic profile. (Am J Obstet Gynecol 2000;183:389-95.)

Key words: C-peptide, epidemiology, glucose, hemoglobin A_{1c}, insulin, oral contraceptives

Abnormalities of glucose metabolism were reported among women who used oral contraceptives shortly after oral contraceptives became widely available in the United States during the early 1960s.[1] Elevated glucose and insulin levels, higher rates of impaired glucose tolerance, and adverse effects on lipids and blood pressure were subsequently found with high-dose contraceptives.[2-5] In response to these effects estrogen dose was steadily decreased with time, and phasic oral contraceptives and formulations containing progestins with greater progestational activity but less androgenicity were introduced.

Large epidemiologic studies of oral contraceptives and glucose metabolism are few. Those that were conducted showed little if any increase in risk of development of type 2 diabetes.[6-8] However, postchallenge glucose levels and the prevalence of impaired glucose tolerance were found to be higher among oral contraceptive users than among nonusers in studies during the 1980s.[9-11] Population-based data from the Second National Health and Nutrition Examination Survey, which was conducted from 1976 to 1980, showed more than twice the prevalence of impaired glucose tolerance among users of oral contraceptives (15.4%) as among nonusers (6.3%).[10] The Second National Health and Nutrition Examination Survey did not ascertain information regarding estrogen dose or type of preparation; however, because of the decline in dose with time, the Second National Health and Nutrition Examination Survey and the other studies cited likely evaluated a mixture of high- and low-dose oral contraceptives, with a greater proportion of high-dose formulations compared with those in current use.

There are currently about 30 oral contraceptive preparations marketed in the United States, and most are low-dose estrogen formulations. Clinical studies assessing low-dose oral contraceptives have primarily concluded that there are clinically insignificant effects on glucose metabolism. This conclusion has been disputed, however, and the studies have been criticized for lack of statistical power and for having been performed almost exclusively in highly selected populations of healthy white women.[2, 12]

To investigate this issue we analyzed data from a large representative population-based survey of US women

17 to 45 years old. We examined whether oral contraceptive use was associated with elevated levels of glycosylated hemoglobin or with elevated fasting glucose, insulin, or C-peptide levels.

Material and methods

Survey design. The Third National Health and Nutrition Examination Survey was conducted from 1988 through 1994 in 89 randomly selected locations throughout the United States.[13] The survey used a stratified multistage probability cluster design to allow generalizability to the noninstitutionalized civilian US population. Participants were interviewed in their homes and given a standardized examination in a mobile examination center; this examination included anthropometric measurements and phlebotomy. Informed consent was obtained from all participants, and the protocol was approved by the institutional review board of the National Center for Health Statistics.

Study population. There were 5482 women aged 17 through 44 years who participated in the home interview. Of these, 325 did not participate in the examination. Also excluded from analyses were women who had never started to menstruate (n = 1), who were currently pregnant (n = 337) or breast-feeding (n = 94), who had undergone a hysterectomy (n = 288) or a bilateral oophorectomy (n = 5), or who had not had a menstrual period in the last 6 months (n = 87). An additional 153 women lacked information enabling us to classify them as never users of oral contraceptives, current users of oral contraceptives, or former users of oral contraceptives, and we were unable to definitively classify 2 women with respect to diabetes status. After these exclusions there were 70 women with diabetes and 4120 women without diabetes.

Oral contraceptive use and covariates. Information on use of oral contraceptives and other reproductive, sociodemographic, and lifestyle characteristics was collected by interview. Women were asked whether they had ever used oral contraceptives and, if so, at what age they had started use, the time since discontinuation, and the duration of use. Current users were queried regarding brand of oral contraceptive. Other interview information included race and ethnicity, parental history of diabetes, last completed year of education, cigarette smoking, number of live births, frequency and amount of alcohol consumed during the last year, and level of physical activity. Intensity of physical activity was based on performance of 9 activities (walking, jogging or running, bicycling, swimming, aerobics, dancing, calisthenics, gardening or yard work, and weight lifting) and was calculated by summing the products of frequency during the last month and intensity rating. Participants were asked to bring to the examination any prescription medications that they were currently receiving. These were recorded and categorized according to indication for use. Body mass index was calculated from measured height and weight (in kilograms per square meter), and waist-hip ratio was calculated from measured waist and hip circumferences.

Laboratory measurements. Hemoglobin A_{1c} (HbA_{1c}) level was measured by a high-performance liquid chromatographic assay, as used in the Diabetes Control and Complications Trial.[14] The upper limit of normal for HbA_{1c} in the assay system was 6.1%, defined as the mean + 2 SD (5.27% + 0.86%) for the group of people with a fasting plasma glucose level <110 mg/dL and a 2-hour postchallenge glucose level <140 mg/dL.

Fasting plasma glucose and fasting serum insulin and C-peptide concentration analyses were limited to the subsample of women who were assigned to be examined in the morning after an overnight fast of ≥8 hours (n = 1639). Plasma glucose level was measured with a hexokinase enzymatic reference method (COBAS MIRA; Roche Diagnostics Corporation, Laboratory Systems, Indianapolis, Ind). The upper limit of normal was 110 mg/dL (mean + 2 SD, 95 mg/dL + 15 mg/dL). Serum insulin level was measured by radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden) and C-peptide level was measured by radioimmunoassay (Bio-Rad Laboratories Inc, Hercules, Calif), both in the Department of Child Health, University of Missouri. The interassay coefficients of variation averaged 8.4% for insulin and 11.2% for C-peptide. Intra-assay coefficients were <10% for both moieties.

Undiagnosed diabetes was defined by a fasting glucose level of ≥126 mg/dL. Impaired fasting glucose was defined by a fasting glucose levels of 110 to 125 mg/dL.[15]

Statistical analysis. Statistical analyses were carried out with SAS software (SAS Institute, Inc, Cary, NC) with appropriate sampling weights. SEs and tests of statistical significance were calculated with SUDAAN,[16] a program that adjusts for the cluster sample design in computing variance. Analysis of covariance was used to adjust means for covariates. In these models values for fasting glucose, insulin, and C-peptide levels were logarithm transformed because of skewed distributions. Variables (see Table III) and squared terms for age and body mass index were tested for statistically significant associations in the multivariate models, and covariates were retained in the final models at a significance level of $P < .10$ to include possible confounders of marginal statistical significance. The final multivariate models included oral contraceptive use, age, race, body mass index, waist-hip ratio, and parental history of diabetes. The model for HbA_{1c} level also included smoking status and alcohol use; the model for fasting insulin level included body mass index squared and alcohol use; and the model for fasting C-peptide level included age squared, body mass index squared, physical activity level, and number of live births.

Table I. Demographic characteristics according to oral contraceptive use category among women without a medical history of diabetes

	Oral contraceptive use		
Characteristic	Never (n = 1070)	Current (n = 803)	Former (n = 2247)
Age (y, mean ± SE)	27.5 ± 0.4	25.8 ± 0.3*†	33.2 ± 0.2
Race and ethnicity (%)			
Non-Hispanic white	58.8	77.6*	73.7
Non-Hispanic black	12.8	11.7	14.2
Mexican American	9.3	5.4*	4.6
Other	19.2	5.2*	7.6
Parental history of diabetes (%)	12.5	10.7†	20.6
History of gestational diabetes (%)	0.8	0.2†	1.4
Body mass index (kg/m², mean ± SE)	25.5 ± 0.5	23.7 ± 0.2*†	25.7 ± 0.2
Waist-hip ratio (mean ± SE)	0.83 ± 0.00	0.81 ± 0.00*†	0.84 ± 0.00
Physical activity level (mean ± SE)	114.1 ± 9.2	114.7 ± 8.0†	97.5 ± 5.0
Cigarette smoking (%)	25.5	28.8†	37.2
Alcohol drinking (%)	37.0	53.9*	50.6
Some college education or more (%)	37.6	49.7*	44.4
Other medication use‡ (%)	2.4	3.7†	6.8
Oral contraceptive use profile			
Duration of use (mo, mean ± SE)	—	65.0 ± 3.3†	49.4 ± 2.1
Age at first use (y, mean ± SE)	—	19.2 ± 0.1	19.5 ± 0.1
Time since cessation of use (y, mean ± SE)	—	—	8.2 ± 0.2

*P < .05, current user versus never user.

†P < .05, current user versus former user.

‡Medications with potential to affect glucose levels, including diuretics, calcium-channel blockers, β-blockers, α-blockers, angiotensin-converting enzyme inhibitors, adrenal corticosteroids, growth hormone, and corticosteroids.

The final models for HbA$_{1c}$, fasting glucose, fasting insulin, and fasting C-peptide levels explained 14.8%, 17.3%, 50.1%, and 43.4% of the observed variance in these variables, respectively.

Results

Among women without diabetes, most were former users of oral contraceptives (57.1%), with equal proportions of those who had never used oral contraceptives (21.4%) and current users (21.6%). Among women with diabetes the proportion of former users of oral contraceptives (75.6%) was even larger, with fewer current users of oral contraceptives (8.8%) than never users of oral contraceptives (15.7%).

Women with diabetes who were receiving insulin were not asked to fast; analyses involving these women were therefore limited to HbA$_{1c}$ level. Among women with diabetes, the HbA$_{1c}$ level among current users of oral contraceptives (mean, 8.87%) was lower than that among those who had never used oral contraceptives (mean, 9.48%; P = .73) but higher than that among former users (mean, 7.66%; P = .47). These differences, however, were not statistically significant because of the large SE for the current users' estimate. The small number of current users with diabetes (n = 5) precluded further investigation of the association between oral contraceptive use and HbA$_{1c}$ level among women with diabetes. The remainder of the analyses therefore focused on the women without diabetes.

Table I presents demographic, lifestyle, medical, and anthropometric factors according to oral contraceptive use. Compared with those who had never used oral contraceptives, current users of oral contraceptives tended to be younger, to be of non-Hispanic white race, to have a lower prevalence of a history of gestational diabetes, to be leaner, to have a lower waist-to-hip ratio, to consume alcohol, and to be more highly educated. Compared with former oral contraceptive users, current users tended to be younger, to have a lower prevalence of a parental history of diabetes and history of gestational diabetes, to be leaner, to have a lower waist-to-hip ratio, to be more physically active, to be less likely to smoke, and to be less likely to be receiving medications with the potential to affect glucose levels. Mean duration of oral contraceptive use was longer among current users than among former users, although mean ages at first use were similar.

Mean HbA$_{1c}$ level was slightly lower among current users of oral contraceptives than among those who had never used oral contraceptives and among former users (Table II). Among current users no trend in HbA$_{1c}$ level was observed with duration of oral contraceptive use, and there was no association with age at which use began. Among former users there was a slight increase in HbA$_{1c}$ levels with a longer time since last use of oral contraceptives. However, this trend was not statistically significant when adjusted for age, body mass index, and other variables. No trend was noted within the first year after cessation of use when this period was subdivided into <1

Table II. HbA$_{1c}$, fasting glucose, fasting insulin, and fasting C-peptide levels according to characteristics of oral contraceptive use among women without a medical history of diabetes

Characteristic	HbA$_{1c}$ level (%)	Fasting glucose level (mg/dL)	Fasting insulin level (pmol/L)	Fasting C-peptide level (pmol/L)
Oral contraceptive use				
Never	5.01 ± 0.03	92.2 ± 0.8	59.8 ± 2.7	621.8 ± 30.6
Current	4.89 ± 0.02*†	86.8 ± 0.6*†	52.6 ± 1.9*	515.5 ± 14.9*†
Former	5.01 ± 0.02	92.1 ± 0.7	57.5 ± 2.1	604.2 ± 20.9
Duration of use among current oral contraceptive users‡				
<1 y	4.90 ± 0.05	85.3 ± 1.4	47.3 ± 5.1	499.4 ± 56.6
≥1 y–<5 y	4.89 ± 0.03	87.8 ± 0.7	56.7 ± 3.9	549.2 ± 29.7
≥5 y–<10 y	4.85 ± 0.04	84.8 ± 0.8	48.6 ± 1.9	487.6 ± 26.8
≥10 y	4.97 ± 0.05	90.2 ± 1.3	55.0 ± 5.8	506.0 ± 53.0
Age started among current oral contraceptive users				
<20 y	4.91 ± 0.02	87.6 ± 0.8	53.8 ± 2.0	548.6 ± 20.7
≥20 y	4.87 ± 0.04	85.5 ± 1.1	50.7 ± 3.5	463.9 ± 28.6§
Time since cessation among former oral contraceptive users‡				
<1 y	4.95 ± 0.03	90.1 ± 0.9	59.8 ± 7.1	601.6 ± 54.0
≥1 y–<3 y	4.98 ± 0.04	90.0 ± 1.6	62.7 ± 4.8	608.8 ± 50.9
≥3 y–<7 y	4.97 ± 0.03	91.2 ± 0.9	53.5 ± 2.7	553.3 ± 29.6
≥7 y	5.06 ± 0.03	93.4 ± 1.0	56.8 ± 2.5	621.4 ± 28.4

Values are mean ± SE.

*P < .05, current users versus never users.

†P < .05, current users versus former users.

‡Statistical significance for duration of use and years since cessation of use were tested with these as continuous variables. Duration was not statistically significantly associated with any of the laboratory variables. Time in years since cessation was positively associated with HbA$_{1c}$ level (P = .0001), but the association became nonsignificant after adjustment for age, body mass index, and other covariates.

§P < .05, ≥20 years versus <20 years.

month, 1 to <3 months, 3 to <6 months, and 6 to <12 months (data not shown). As with HbA$_{1c}$ level, mean fasting glucose, insulin, and C-peptide levels were slightly lower among current users than among those who had never used oral contraceptives or former users. Values for those who had never used oral contraceptives and for former users were not significantly different from each other. The pattern of relationships demonstrated for HbA$_{1c}$ level among the 3 oral contraceptive use groups were generally in the same direction for fasting glucose, insulin, and C-peptide levels.

Prevalence of impaired fasting glucose was lower among current users of oral contraceptives (0.2%) than among those who had never (2.9%; P = .12) or formerly (1.6%; P = .007) used oral contraceptives. Similarly, prevalence of previously undiagnosed diabetes was lower among current users (0.1%) than among those who had never used (0.6%; P = .07) or those who had formerly used (0.7%; P = .08) oral contraceptives. Small numbers of cases precluded further examination of the relationship of oral contraceptive use with impaired fasting glucose and undiagnosed diabetes.

Mean HbA$_{1c}$ and fasting glucose, insulin, and C-peptide levels are presented in Table III according to selected characteristics. HbA$_{1c}$ level increased with age and was highest among non-Hispanic blacks, followed by Mexican Americans, with the lowest levels observed

among non-Hispanic whites. Mean HbA$_{1c}$ level was higher among women with a parental history of diabetes, those with a body mass index ≥25 kg/m^2, and those who were above the median value for waist-hip ratio and below the median physical activity level. HbA$_{1c}$ level was also higher among current smokers, nondrinkers, and less-educated women. The relationships of these characteristics with fasting glucose level were generally similar to those observed for HbA$_{1c}$ level, although mean fasting glucose level was highest among Mexican Americans rather than non-Hispanic blacks. The patterns for fasting insulin and fasting C-peptide levels were of similar direction but more pronounced than those observed for HbA$_{1c}$ and fasting glucose levels.

Fig 1 presents age-adjusted and multivariate-adjusted geometric means for HbA$_{1c}$ and fasting glucose, insulin, and C-peptide levels. Multivariate adjustment attenuated the age-adjusted differences in HbA$_{1c}$ level among the 3 oral contraceptive use categories. The lower age-adjusted mean for current users compared with those who had never used oral contraceptives was not statistically significant after multivariate adjustment (P = .19), nor was the difference between current and former users (P = .50). After adjustment the mean fasting glucose level among current oral contraceptive users remained significantly lower than levels among women who had never used oral contraceptives (P = .002) and

Table III. HbA$_{1c}$, fasting glucose, fasting insulin, and fasting C-peptide levels according to selected characteristics among women without a medical history of diabetes

Characteristic	HbA$_{1c}$ level (%)	Fasting glucose level (mg/dL)	Fasting insulin level (pmol/L)	Fasting C-peptide level (pmol/L)
Age				
17-30 y	4.93 ± 0.02	88.3 ± 0.4	55.4 ± 1.5	561.7 ± 14.6
31-44 y	5.05 ± 0.03*	93.4 ± 0.8*	57.7 ± 2.2	606.9 ± 23.2
Race and ethnicity				
Non-Hispanic white	4.93 ± 0.02*	90.7 ± 0.6	51.3 ± 1.6	555.7 ± 15.9
Non-Hispanic black	5.21 ± 0.02*	91.9 ± 1.0	71.5 ± 3.1*	627.1 ± 22.9
Mexican American	5.13 ± 0.02*	93.9 ± 0.9*	73.9 ± 2.1*	747.7 ± 21.1
Parental history of diabetes				
Negative	4.95 ± 0.02	90.1 ± 0.3	53.4 ± 1.3	557.0 ± 13.4
Positive	5.17 ± 0.04*	96.5 ± 1.7*	72.3 ± 4.3*	730.7 ± 41.0
Body mass index				
≤25 kg/m^2	4.91 ± 0.02	88.5 ± 0.5	41.4 ± 0.7	427.5 ± 11.0
>25 kg/m^2	5.11 ± 0.03*	95.0 ± 0.9*	78.1 ± 2.6*	811.8 ± 26.1
Waist-hip ratio				
≤0.81 (median)	4.91 ± 0.03	88.3 ± 0.5	43.2 ± 0.9	429.5 ± 12.2
>0.81 (median)	5.05 ± 0.02*	93.4 ± 0.7*	66.7 ± 2.4*	703.5 ± 22.2
Physical activity level				
≤60.6 (median)	5.03 ± 0.03	92.2 ± 0.8	62.0 ± 1.9	652.3 ± 17.3
>60.6 (median)	4.94 ± 0.02*	90.2 ± 0.4*	51.7 ± 1.9*	525.8 ± 16.6
Cigarette smoking				
Nonsmoking	4.96 ± 0.02	90.9 ± 0.5	56.6 ± 1.9	563.9 ± 16.0
Current smoking	5.03 ± 0.02*	91.0 ± 0.6	56.3 ± 2.4	633.0 ± 28.6
Alcohol intake				
Nondrinking	5.05 ± 0.02	91.9 ± 0.7	64.0 ± 2.8	639.6 ± 23.3
Drinking	4.92 ± 0.03*	90.2 ± 0.4*	50.0 ± 1.7*	539.3 ± 19.5
Education				
High school graduate or less	5.02 ± 0.02	91.9 ± 0.7	63.1 ± 1.9	654.3 ± 18.4
Some college or more	4.95 ± 0.03*	90.5 ± 0.6	50.3 ± 1.9*	519.3 ± 20.9
Other medications†				
Not receiving	4.99 ± 0.02	91.2 ± 0.5	56.3 ± 1.5	580.9 ± 13.5
Receiving	5.04 ± 0.05	91.1 ± 0.8	63.3 ± 4.2	688.1 ± 47.7

Values are mean ± SE.

*$P < .05$, comparison of laboratory values by characteristic. All 3 race and ethnic groups were significantly different from one another in HbA$_{1c}$ and C-peptide levels, Mexican Americans and non-Hispanic whites were significantly different in glucose level, and non-Hispanic whites were different from non-Hispanic blacks and Mexican Americans for insulin level.

†Medications known to affect glucose levels, including diuretics, calcium channel blockers, β-blockers, α-blockers, angiotensin-converting enzyme inhibitors, adrenal corticosteroids, growth hormone, and corticosteroids.

among former users ($P = .04$); however, the differences in levels were only 3.0 and 2.3 mg/dL, respectively. The associations of fasting insulin and fasting C-peptide levels with oral contraceptive use were not statistically significant in either the age-adjusted or the multivariate-adjusted models.

Duration of oral contraceptive use among current users and time since last use among former users were not associated with any of the 4 indicators of glucose metabolism after multivariate adjustment (data not shown). The results for oral contraceptive use shown in Fig 1 were similar when the multivariate models were rerun with 212 women (5%) excluded whom we identified as receiving any medication that might affect glucose metabolism (eg, diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers, β-blockers, α-blockers, adrenal corticosteroids, and nasal corticosteroids). The adjusted differences between current users and those who had never used oral contraceptives for fasting glucose level were similar when examined by strata of race or ethnicity,

parental history of diabetes, age, and body mass index (data not shown).

A total of 41.3% of women who were currently using oral contraceptives were using triphasic formulations, the vast majority (95.0%) were using formulations containing <0.05 mg estrogen, and <1% were using progestin-only formulations. There was no difference in multivariate-adjusted mean fasting glucose level between users of triphasic preparations and monophasic preparations ($P = .48$). The two most common preparations were a triphasic formulation containing 0.035 mg ethinyl estradiol and 0.5, 0.75, and 1 mg norethindrone (23.9%) and a monophasic formulation containing 0.035 ethinyl estradiol and 1 mg norethindrone (20.7%). There was no difference in adjusted mean glucose level between users of these preparations ($P = .62$).

Comment

In this large population-based study HbA$_{1c}$ and fasting glucose, insulin, and C-peptide levels were slightly lower among current users of oral contraceptives. These
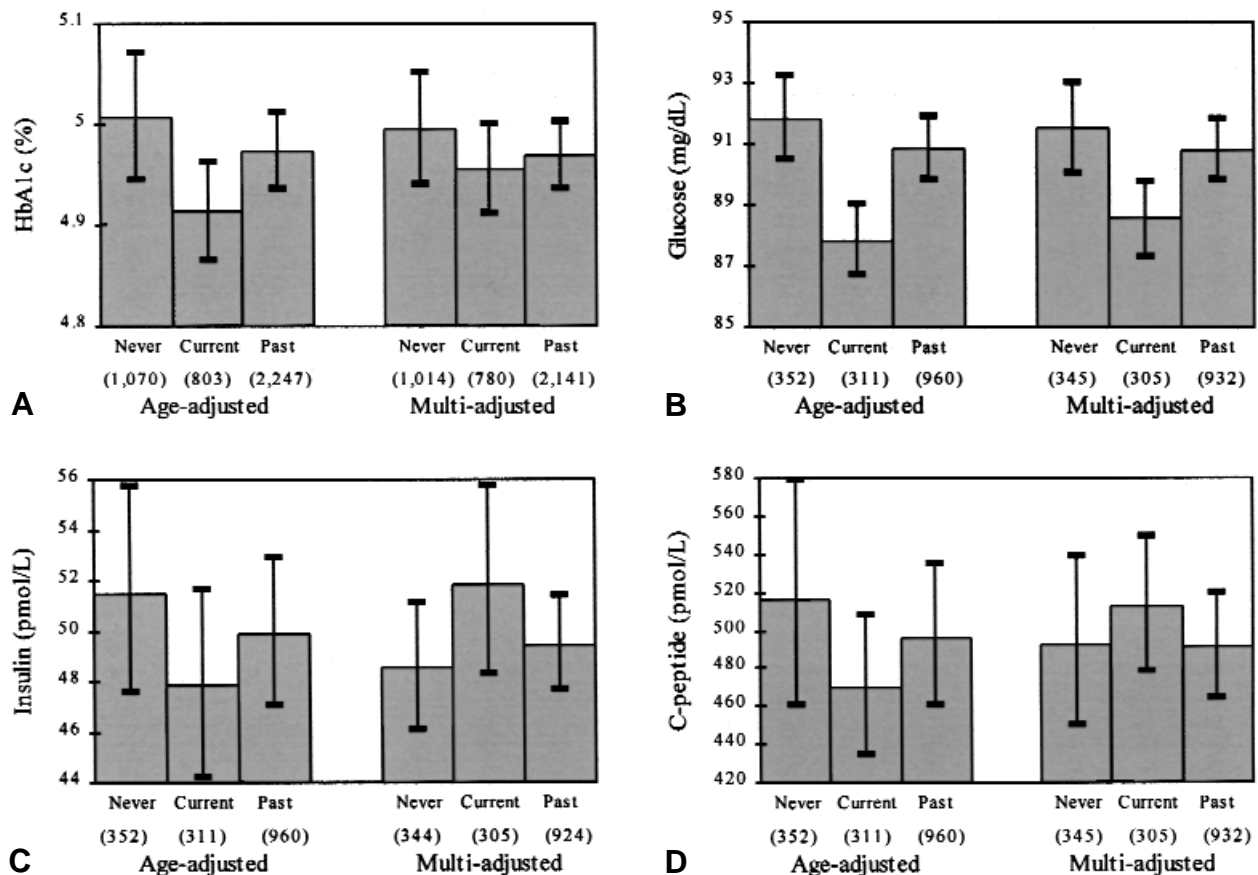
Fig 1. Age-adjusted and multivariate-adjusted means for HbA$_{1c}$ **(A)**, fasting glucose **(B)**, fasting insulin **(C)**, and fasting C-peptide **(D)** levels according to oral contraceptive use among women without a medical history of diabetes. *Numbers in parentheses,* Numbers of subjects; numbers vary according to study sample used in analysis and missing values for covariates included in regression models. $P > .2$, all comparisons except age-adjusted HbA$_{1c}$ level for current users versus those who had never used oral contraceptives ($P = .002$); age-adjusted fasting glucose level for current users versus never users ($P < .0001$) and former users *(Past)* ($P = .0004$) of oral contraceptives; and multivariate-adjusted fasting glucose for current users versus never users ($P = .002$) and former users ($P = .004$) of oral contraceptives.

women, however, also tended to have more favorable values of other factors that influence glucose metabolism, such as body mass index and waist-hip ratio. After adjustment for these and other factors, means for current users became more similar to the values for those who had never used oral contraceptives and for former users. Only the slightly lower levels of fasting glucose among current oral contraceptive users (difference of approximately 3 mg/dL) remained statistically significant.

The cross-sectional design of the Third National Health and Nutrition Examination Survey presents limitations in assessing a causal relationship between oral contraceptives and glucose metabolism. Specifically, the lower HbA1c, glucose, insulin, and C-peptide levels among current users could be the result of a selection process. Potential users of oral contraceptives may have been screened to exclude women with an adverse glycemic risk profile, and lower values among current

users may have occurred because women in whom hyperglycemia developed had discontinued use before the survey. The healthier risk factor profile and lower prevalence of gestational diabetes, impaired fasting glucose, and undiagnosed diabetes among current users provides some support for this hypothesis. However, women who had recently stopped using oral contraceptives did not have elevated glucose values, which suggests that discontinuation was not the result of development of irreversible abnormalities in glucose metabolism. Also, duration of use among current users was not associated with any of the outcomes examined, which supports the conclusion that oral contraceptive formulations currently used by US women do not affect glucose and insulin metabolism.

The final models for HbA$_{1c}$ and fasting glucose levels explained only 14.8% and 17.3% of observed variance, respectively, which reflects how tightly regulated these physiologic parameters are. Another explanation for the

low R^2 may be that some explanatory factors, such as genetic variation, could not be considered in the multivariate models. Measurement error in the independent variables, especially if true variation in HbA_{1c} and fasting glucose levels were small, could have lowered R^2 also. In contrast, the models for fasting insulin and C-peptide levels explained nearly half the observed variance in these outcomes (50.1% and 43.4%, respectively). The relatively large R^2 values for the insulin and C-peptide models argue against measurement error.

Our results for fasting glucose level are consistent with those of the 1976 through 1980 National Health and Nutrition Examination Survey and of community-based studies, which have observed slightly lower levels among oral contraceptive users than among nonusers (between 0.8 and 5.1 mg/dL lower, compared with 3.0 mg/dL in our study).[9-12, 17, 18] Our results for HbA_{1c} level agree with those of a study conducted in France, which found no difference between oral contraceptive users and nonusers.[11] In that study fasting insulin levels were significantly higher among oral contraceptive users than among nonusers. Our data showed higher fasting insulin and C-peptide levels, after adjustment for potential confounders, among current oral contraceptive users than among those who had never used oral contraceptives, although the differences were small (3.3 and 19.8 pmol/L, respectively) and not statistically significant.

Nearly all the oral contraceptive users surveyed were using low-dose estrogen formulations, and almost half were using two specific combination oral contraceptive formulations. We found no differences between triphasic and monophasic formulations or between the two most common formulation types. Previous work has noted differences in effects on carbohydrate metabolism according to progestin type. We were unable to assess the various progestin types, because nearly half of the women took norethindrone and the remainder took a variety of other preparations with different progestin types. Greater associations of norgestrel with postchallenge glucose level and modest or no effects of other progestins were found in one study[9]; in another, increases in incremental glucose, insulin, and C-peptide areas under the dose-response curves were most pronounced with monophasic levonorgestrel combinations, followed by desogestrel and norethindrone.[19] The latter findings were corroborated in a study showing that associations with glucose, insulin, and C-peptide levels after intravenous glucose tolerance test were strongest for levonorgestrel, followed by desogestrel and norethindrone.[20] These studies suggest that norethindrone, the most commonly used progestin type in our study, is one of the least potent types, which possibly explains the lack of association that we found. The possibility that specific formulations have adverse effects on glucose metabolism in certain high-risk groups cannot be eliminated because of our inability to assess all formulations.

These US population-based data indicate that current users of oral contraceptives as a group do not have elevations in measures of glucose and insulin metabolism, and the data are consistent with no adverse effect of these formulations. These results are thus reassuring regarding the present state of health of US women who use oral contraceptives.

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